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(21) International Application Number: PCT/GB96/00073 (22) International Filing Date: 16 January 1996 (16.01.96) (30) Priority Data: 9500863.7 17 January 1995 (17.01.95) GB (71) Applicant (for all designated States except US): GRAMPIAN PHARMACEUTICALS LIMITED [GB/GB]; Marathon Place, Moss Side Industrial Estate, Leyland, Lancashire PR5 3QN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): LAVERY, Martin [GB/GB]; 53 Powis Road, Ashton-on-Ribble, Preston, Lancashire PR2 1AD (GB). (74) Agent: MANATON, Ross, Timothy; JY & GW Johnson, Furnival House, 14-18 High Road, London WC1V 6DE (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: MEDICATED ANIMAL FOODSTUFFS**(57) Abstract**

A method of adding a medicament (or other added ingredient) to animal feed pellets is described, in which the medicament is contained in a cohesive gel which is mixed with the feed pellets. The gel coats the pellets substantially homogeneously, and leaves little contamination of the mixing vessel. Preferably, the gel has a viscosity in the range 5,000 to 20,000 cP, and is added to the feed pellets in an amount of between 2 and 40 kg/tonne.

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MEDICATED ANIMAL FOODSTUFFS

This invention relates to methods for incorporating feed ingredients (particularly, but not exclusively, medicaments) with animal foodstuffs, and to substances
5 useful in such methods.

Treatment of intensively farmed animals with medication is often carried out by "mass medication", that is to say that animals are not treated individually, but as a group. The most efficient way of doing this is by adding
10 the treatment to the animals' feed or drink. Water medication is very labour intensive and may require veterinary supervision, and longer term treatments are much more easily carried out by supplying the group of animals with medicated feed.

15 Manufactured foodstuffs for animals such as cattle, pigs, and fowl are usually provided in the form of pellets or similar particulate material. Pellets are typically manufactured by combining a cereal base with ingredients such as oil and protein, steam conditioning the mixture (for
20 example at 70°C for 5 minutes), extruding through a circular die (typically between 2mm and 15mm in diameter), cutting into appropriately sized lengths (eg. 5-20mm), and drying. The finished pellets are generally cylindrically shaped, having a relatively smooth surface, and a density typically
25 of about 1.2g.cm⁻³.

Conventionally, additives such as drugs are incorporated into the feed mixture before the extrusion step. However, because many different drugs are required to be added to feed pellets from time to time, and because the
30 demand for any particular medicated product is generally relatively low compared to the demand for non-medicated feed, it is not usually viable to provide dedicated plant for manufacturing specific products. Instead, batches of medicated feed are manufactured according to need using
35 machinery otherwise used to produce non-medicated feed. A

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major problem with this manufacturing regime is that the plant needs to be completely cleaned down after the production of each batch of medicated feed, in order to reduce the risk of contaminating subsequent feed batches. This obviously reduces efficiency and increases operating costs.

The addition of active agents to individual batches of feed could be carried out more cost-effectively "off-line", that is to say with non-medicated feed pellets being manufactured continuously, and those batches which require medication being transferred to a separate plant for addition of medicament.

This would require the application of the medicament to the surfaces of the finished pellets, and attempts have been made to accomplish this in the past. However, no reliable technology currently exists to enable medications to be routinely and reproducibly added to the external surface of feed pellets and to remain there during transport and use.

It has now surprisingly been found that reliable homogeneity of active ingredient in the finished feed can be achieved by coating the pellets with a cohesive gel containing the active ingredient. It has furthermore been surprisingly found that gel coating according to the invention tends to leave the feed mixing vessel in which the coating is carried out substantially free from active agent contamination. Because the coating method is not dependent upon the nature of the active ingredient, the invention will also be of use in adding other substances (such as nutritional supplements), and added ingredients in general.

The present invention therefore provides, in one aspect, a method of incorporating an added ingredient with an animal foodstuff, comprising the step of coating feed pellets (or similar particulate foodstuff material) with a cohesive gel containing said added ingredient.

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In some instances, the pellets may be fed to animals directly after coating, but more commonly the gel is dried or absorbed into the pellet, thus entrapping the medication in the pellet and giving protection against attrition and the formation of active agent dust.

In this specification, the term "gel" is to be understood as referring to any viscous cohesive suspension, and the term "gelling agent" to any thickening agent capable of producing such a suspension. The gel is preferably a highly viscous solution or suspension (for example an aqueous suspension), having low flow and good adhesive properties. Thixotropic gels may be used. For the gel to behave as mentioned above, the viscosity should be controlled within the range 5,000 to 20,000 cP (Brookfield RV, spindle 6, 25 rpm, 20°C), more preferably in the range 5,000 to 15,000 cP, and ideally in the range 7,500 to 12,500 cP. This viscosity range allows added ingredients having particles of a wide variety of sizes and densities to be homogeneously suspended, and also gives the gel the necessary cohesive properties for good feed pellet distribution and low mixer contamination.

Examples of suitable gelling agents which may be used for this purpose are modified cellulose polymers, synthetic polymers, natural polysaccharides, clays, proteins and colloidal silica, but other gelling agents may also be used. The gel can be supplied to users ready mixed with the added ingredient(s), or as a raw gel, for such ingredient(s) to be added. Alternatively, the gelling agent may be provided in powder form and made up to the finished gel when required, with the added ingredient(s) being either mixed in at the outset, or being added after the gel is made up. If the gelling agent is supplied in powder form, the mixing can be accomplished by adding water, oil, or another appropriate liquid, and mixing vigorously (for example in a high speed planetary mixer) to shear the mixture and allow complete hydration of the gelling agent. The amount of liquid will depend on the gelling agent used, and on the ratio of

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gelling agent to other ingredients in the powder; typically the final gel will contain 1 to 50% w/w (preferably 1 to 10% w/w) of the gelling agent.

Examples of suitable modified cellulose polymers which may be used as the gelling agent are: sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxyethylcellulose, and microcrystalline cellulose.

10 Examples of suitable synthetic polymers are: polyacrylic acid polymers (Carbomers), polyvinylpyrrolidones (PVPs), crospovidones, polyvinyl alcohols, and colloidal anhydrous silicas.

15 Examples of natural polysaccharides which may be used include: xanthan gum, acacia gum, agar, carrageenan and tragacanth.

Examples of suitable clays are bentonite and aluminium magnesium silicates, and an example of a suitable protein is gelatin.

20 The invention may be used to incorporate many different types of added ingredient or combinations of added ingredients. Examples of medicaments which may be used are: antimicrobials (such as tetracyclines, penicillins, sulphonamides, cephalosporins, cephamycins, aminoglycosides, aminocyclitols, trimethoprim, dimetridazole, erythromycin, framycetin, furazolidone, lincosamides, tiamulin, macrolides, and streptomycin); antiprotozoals (such as clopidol, monensin, salinomycin, narasin, halofuginone, lasalocid, amprolium, maduramicin, and robenidine); and
25 antiparasitics (such as benzimidazoles, imidazothiazoles, avermectines, milbermycins, salicylicanilides and piperazine).

Examples of other added ingredients are growth

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promoters (such as tylosin, virginiamycin, zinc bacitracin, avoparcin, bambamycin, avilamycin); vaccines (for example to prevent *E.coli* infections); immunostimulants; vitamins (such as vitamin A, B group vitamins, vitamins C, D, E and K3);
5 minerals (for example salts containing micronutrients, such as iron, zinc, copper, selenium, iodine, manganese, calcium and phosphorus); and enzymes. The concentration of total added ingredients in the gel will typically range from 0.5 to 10% w/w of the final gel.

10 Many products may also require a preservative (typically in a concentration of 0.05-5% w/w of the final gel), to prevent the growth of organisms in use. Examples of suitable preservatives are: parabens, benzoic acid and salts, propionic acid and salts, sorbic acid and salts,
15 bronopol and formaldehyde.

The final formulations of the products may also include other adjuvants such as dispersing or wetting agents (such as surfactants e.g. Tweens, Brij's, sodium lauryl sulphate), buffering agents (such as citric acid and
20 citrates, phosphoric acid and phosphates) and diluents (such as lactose, calcium carbonate, silica and starch).

The feed pellets and gel are preferably mixed relatively gently, to prevent the feed from disintegrating. Any low shear mixer with a blade which has a fine tolerance
25 with the side of the mixing vessel is adequate, such as a planetary mixer or ribbon blender. The gel is gently added to (e.g. folded into) the feed pellets and slowly and uniformly coats them. The amount of gel added per tonne of feed appears to be critical and should be in the range 2-
30 40kg/tonne. Less than 2kg/tonne gives poor product homogeneity, and over 40kg/tonne gives rise to damp (i.e. overly wetted) feed and possible mould growth in the finished feed pellets; more typically the amount used is in the range 5-20kg/tonne, and in many cases the amount is more
35 than 10kg/tonne.

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The following are three practical examples, illustrating the invention:

Example 1

Ingredients of powder

5	Chlortetracycline (15% Feed grade)	2.67kg
	Sodium carboxymethylcellulose (high viscosity grade) (Blanose 7HF, Aqualon, France)	0.50kg
	Lactose	0.81kg
	Potassium Sorbate	0.02kg

- 10 All ingredients are thoroughly blended dry in a planetary mixer for 12 minutes, and the product transferred into polythene-lined sachets and heat-sealed. The product is used by adding sufficient water to a mixing vessel (eg. planetary mixer bowl) so that the suspending agent forms a
- 15 2.5% w/v solution. (For example, 1kg of product is blended with 5 litres of water.) The suspension is formed by mixing vigorously for 10 minutes.

- Once the product is suspended and the gel is sufficiently hydrated it is ready to coat the feed pellets.
- 20 The pellets are weighed into a suitable mixer (eg ribbon blender) and the required amount of gel added to give the medication level required (eg for 400 mg/kg, add 20 litres/tonne). The mixture is blended for 5 minutes and dispensed into paper sacks.

- 25 In a test, the resultant coated feed, when analysed for chlortetracycline content, gave a mean value of 412.6 mg/kg, with a coefficient of variation over 10 assays of 4.6%. The amount of contamination of the mixer as a percentage of the total chlortetracycline added was 0.023%.

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Example 2Ingredients of powder

Sulphadiazine	0.25kg
Trimethoprim	0.05kg
5 Sodium carboxymethylcellulose (high viscosity grade) (Walocel CRT 30000 PA, A. Branwell, England)	0.50kg
Lactose	1.20kg

The product is prepared by dry blending as in Example 10 1. The suspension is formed by mixing 2kg of product with 20 litres of water as above. To obtain 300mg/kg of combined actives in the feed, 20 litres of gel is added per tonne of feed, and blended for 5 minutes.

The coated pellets produced by these methods are found 15 to have even distribution of medicament and good durability upon handling. The mixing vessel becomes coated with gel only to a minimal extent.

Example 3Ingredients of gel

20 Potassium penicillin V	0.14kg
Colloidal anhydrous silica (Aerosil 200, Degussa Ltd)	0.20kg
Dewaxed Sunflower seed oil	3.66kg

The product is prepared by mixing the silica 25 thoroughly with the oil to form a viscous gel base. Then the penicillin is blended into the mixture by using a high shear blender over 20 minutes. The product is packed into polypropylene pails and allowed to reach maximum viscosity. After 24 hours standing the viscosity is 18000cP (Brookfield 30 RV, spindle 6, 25rpm, 20°C).

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In a full scale test mix approximately 1.5kg of product was added to 450kg of feed pellets in a paddle mixer and mixed for 1 minute.

The result of the mean assay of ten subsamples of the 5 coated feed was 106.2mg/kg (106.2% of nominal) with a coefficient of variation of 6.8%

The amount of contamination of the mixer was quantified as 0.007% of the total drug added.

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CLAIMS

1. A method of incorporating an added ingredient with an animal foodstuff, comprising the step of coating feed pellets (or similar particulate foodstuff material) 5 with a cohesive gel containing said added ingredient.

2. A method according to claim 1, in which the gel contains a gelling agent in an amount of between 1 and 50% w/w of the final gel.

3. A method according to claim 2, in which the 10 amount of gelling agent is between 1 and 10% w/w of the final gel.

4. A method according to claim 2 or claim 3, wherein the gelling agent is a modified cellulose polymer, a synthetic polymer, a natural polysaccharide, a clay, a 15 protein, or colloidal silica.

5. A method according to any of claims 2 to 4, wherein the gel is manufactured by mixing a powder comprising said gelling agent and said added ingredient with a solvent or suspension medium, such as water or oil.

20 6. A method according to any preceding claim, wherein said added ingredient is a medicament (such as an antimicrobial, an antiprotozoal, or an antiparasitic), a growth promoter, a vaccine, a mineral, a vitamin, an immunostimulant or an enzyme, or any combination of such 25 ingredients.

7. A method according to any preceding claim, wherein the gel is added to and mixed with the feed pellets in a quantity of between 2 and 40 kg/tonne.

8. A method according to claim 7, wherein the amount 30 of gel used is in the range of 5 to 20 kg/tonne.

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9. A powder mixture comprising a gelling agent and an ingredient (such as a medicament) to be added to an animal foodstuff, suitable for use in a method according to claim 5.

5 10. A method of incorporating an added ingredient with an animal foodstuff in the form of pellets (or similar particulate foodstuff material), suitable for feeding to animals such as cattle, pigs and fowl, the method comprising the steps of:

10 placing a quantity of said pellets (or other particular foodstuff material) in a suitable mixing vessel;
adding to said vessel a cohesive gel in a quantity of between 2 and 40kg per tonne of pellets (or other particulate foodstuff material), said gel containing said
15 added ingredient and having a viscosity of at least 5,000cP;
and

mixing said gel with said pellets (or other particulate foodstuffs material) so that the latter become substantially homogeneously coated with said gel.

INTERNATIONAL SEARCH REPORT

Int: nal Application No
PC1/GB 96/00073

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23K1/00 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A23K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP,A,0 231 817 (GEBRÜDER BÜHLER) 12 August 1987 see column 3, line 28 - line 49 see claims 1,4,5 ---	1-10
X	PATENT ABSTRACTS OF JAPAN vol. 9, no. 125 (C-283), 30 May 1985 & JP,A,60 012939 (KANEAFUCHI KAGAKU KOGYO KK), 23 January 1985, see abstract ---	1-10
A	US,A,3 639 637 (JAMES A. CAMPBELL) 1 February 1972 see column 2, line 3 - line 29 ---	1
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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